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THE ETIOLOGY AND EXPERIMENTAL PRODUCTION OF HERPES ZOSTER*

WITH PLATES 8 TO 19

EDWARD C. ROSENOW AND SVERRE OFTEDAL

*From the Memorial Institute for Infectious Diseases, Chicago, and The Mayo Foundation,
Rochester, Minnesota*

In our preliminary note¹ we reported the production of herpes of the skin, tongue, and lips, and of lesions in the corresponding ganglia, in a large number of animals injected with streptococci isolated from the tonsils, the pyorrheal pockets, the sputum, and the spinal fluid in herpes in man. In this paper, we wish to review briefly the development of our knowledge of herpes, record the results of the cultures and other findings in the cases studied, give details of representative experiments, and discuss the significance of our results.

HISTORICAL REVIEW

The first reliable report of observations concerning the etiology of herpes zoster was that of von Bärensprung² in 1861. He advanced the theory of a nervous origin, and later³ demonstrated an acute inflammatory condition of the ganglion corresponding to the region affected. C. Boeck, in 1878, demonstrated pus-infiltration of the gasserian ganglion in the case of a girl who died with meningeal symptoms and in whom herpes of the face had developed. Wyss⁴ and Sattler⁵ each reported a case of zoster of the ophthalmic branch of the trigeminal nerve. In the case reported by Wyss, in which death occurred 7 days after the appearance of the eruption, hemorrhages were noted in and around the gasserian ganglion; there was interstitial "purulent inflammation" of the ganglion together with small abscesses of the eye muscles. In Sattler's case, with death 14 days after the eruption, there were round-cell infiltration of the ganglion, destruction of the ganglion cells, and degeneration of the ophthalmic nerve, the other two branches of the trigeminal nerve being normal. Lesser⁶ reported 3 cases of zoster of the trunk in which degenerative changes and hemorrhages were within and surrounding the ganglia corresponding to the area of herpes. In 1900 the classic work of Head and Campbell⁷ appeared in which the etiology of herpes zoster was thoroughly considered on the basis of pathologic findings in 15 autopsies and 400 clinical cases which had come under Head's⁸ observation during his notable work on the subject of referred pain in visceral diseases. They concluded that herpes zoster is a specific infec-

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¹ Jour. Am. Med. Assn., 1915, 64, p. 1968.

² Ann. d. Char. Krankenh., Berl., 1861, 9, p. 40.

³ Ibid., 1862, 10, p. 37; 1863, 11, p. 96.

⁴ Arch. d. Heilk., 1871, 16, p. 261.

⁵ Irish Hosp. Gaz., 1874, 2, p. 199.

⁶ Arch. f. path. Anat., 1881, 86, p. 391.

⁷ Brain, 1900, 23, p. 353.

⁸ Ibid., 1893, 16, 1; 1894, 17, p. 339.

tious disease which confers immunity, the number of recurrences being between 1 and 2%; that the specific virus has an affinity for the nervous system, particularly for the ganglia, in which there are found inflammatory changes, acute or chronic, according to the length of time between the appearance of the eruption and death. They proposed to consider the disease as an acute posterior poliomyelitis, in contradistinction to acute anterior poliomyelitis. They were unable to demonstrate micro-organisms in the affected ganglia. There is much other evidence tending to prove the infectious nature of the disease. As early as 1892, Head described a form of herpes as an acute specific infection. Blaschko⁹ corroborated many of the findings of Head and Campbell, and described several cases of herpes zoster with febrile disturbances and swelling of the regional lymphatic glands. Oppenheim¹⁰ cited the case of a young man with a bilateral zoster in the ulnar region which was accompanied by severe swelling of the glands. He stated also that epidemics of the disease had been reported; notably, those cited by Oppenheim, by Rohi, Kaposi, Weis, Reily, and Dopter—in the latter instance a house epidemic. Sachs¹¹ reported an epidemic that occurred in Breslau.

Micro-organisms (diplococci) were demonstrated in the spinal fluid by Achard and Loeper, Widal, and Brissaud-Siccard (Oppenheim). Magnus¹² reported a case which is interesting in view of our experimental observations. The patient, a man 41 years of age, had had an attack of rheumatism 6 years before his last illness; otherwise he had been well. His last illness was marked by grave motor disturbances and 3 weeks before death there developed a herpes zoster over the left side of the chest. Of the 20 spinal ganglia examined, pathologic changes were found only in the 3rd dorsal; hemorrhages were visible macroscopically, while microscopically there was an engorgement of the blood vessels and these were surrounded by marked areas of round-cell infiltration, which were continued into the periphery of the ganglion. In the ganglion proper there were hemorrhages and areas where only remnants of the ganglion cells remained. The round-cell infiltration was especially marked in the periphery, about the blood vessels. It was not diffuse, but occurred in small circumscribed areas. A painstaking search failed to reveal any micro-organisms in the ganglia. The findings in the cord were significant. In the 2nd and 8th cervical, and in the 1st, 2nd, 3rd, 5th, and 6th dorsal segments there were found circumscribed areas of round-cell infiltration, especially marked about the arteria centralis and its anterior-horn ramifications. In the 2nd dorsal segment in the center of the anterior horn within an area of round-cell infiltration adjacent to an engorged blood vessel, diplococci were demonstrated. Finally, Sunde¹³ reported a case of ophthalmic herpes in which he found diplococci in the hemorrhagic gasserian ganglion.

Howard¹⁴ showed that the reaction of the skin in simple herpes does not differ essentially from that in zoster, and that simple herpes of the skin about the nose and the lips, like herpes of the trunk in pneumonia and meningitis, is associated with lesions of the Gasserian and the spinal ganglia.

Trevisanillo¹⁵ isolated pneumococci from the vesicles in herpes of the lips in 4 cases of pneumonia, and reproduced vesicular lesions by inoculating the organism in normal areas of skin in the same individual. The virulence of

⁹ Arch. f. mikros. Anat., 1887, 30, p. 495. Arch. f. Dermat. u. Syph., 1894, 42, p. 295.

¹⁰ Textbook of Nervous Diseases, 1911, 1, p. 574.

¹¹ Rev. prat. d. mal. cutan., 1907, 6, pp. 9, 49.

¹² Norsk. Mag. f. Laegevidensk., 1906, 4, p. 1429.

¹³ Ibid., 1913, 11, p. 339.

¹⁴ Amer. Jour. Med. Sc., 1903, 125, p. 256.

¹⁵ Ann. dell' Inst. Maragliano, 1914, 7, p. 277.

the pneumococci was low, but could be increased with successive animal passages (white mice). Since pneumococci were recovered from the blood also, there is no reason to doubt the occurrence of lesions in the ganglia in these cases.

That herpes occurs in the mucous membranes of the viscera, the respiratory and digestive systems, and the kidneys has been the belief of some close clinical observers. Fernet¹⁶ cited several cases in which the relation between visceral disturbances and a concomitant herpes zoster was very striking, this being particularly true of pharyngitis of a certain type ("angine herpetique") and fibrinous pneumonia. Fernet believed that the former was due to an inflammation of the glossopharyngeal nerve and the latter to lesions along the vagus and the sympathetic, affecting the peripheral nerve-endings which ramify in one or more lobes of the lungs. He called attention to the fact that herpes labialis, so commonly found in these diseases, occurs invariably on the same side as that on which the pneumonia or angina is found. As evidence of the occurrence of herpes in the digestive tract, he cited among other cases the following: A 5-year-old boy was seized in the evening with high fever, accompanied by severe chills, which continued throughout the night. In the morning the temperature was lower, but a marked angina was present, which subsided the following day. Two days later there was a similar attack of fever, this time followed by a marked herpes of the face, the neck, the trunk, and the extremities. The second day of this attack the patient had colic, with a profuse discharge of mucus and slightly blood-tinged stools. These attacks lasted 3 days and then the symptoms disappeared, together with the herpes of the skin. The evidence seems strongly in favor of a herpes of the lower bowel.

Bittorf,¹⁷ Kanera,¹⁸ Rosenberg,¹⁹ and Rosenbaum²⁰ reported cases of renal colic appearing simultaneously with a herpes zoster corresponding to the affected kidney. Vetleson²¹ cited a case in which there was apparently a herpes of the lower intestinal tract, the patient, on the second day after the eruption of an inguino-femoral zoster, complaining of a similar pain associated with colic in the lower abdomen. In this case cultures were made, and from the herpetic vesicles and the spinal fluid a gram-positive non-encapsulated diplococcus was isolated. Vetleson cited another interesting case in which pneumonia, meningitis, appendicitis, and herpes facialis occurred concomitantly. He considered this an illustration of a spread of the infection along the nerve trunks upward through the cervical ganglion to the meninges, and downward along the vagus and the sympathetic to the lungs and the appendix.

Hunt²² suggested that the attacks of vomiting and slow irregular pulse in a case of herpes of the ear were probably due to involvement of the vagus. However, postmortem records in which lesions of the visceral nerves of the ganglia have been demonstrated, cannot be found.

The finding of diplococci in the blister fluid, in the spinal fluid, and in the ganglia in these isolated instances suggests strongly that herpes zoster is a streptococcus infection. The necessary experimental proof, however, has heretofore not been brought forward.

¹⁶ Semaine méd., 1910, 30, p. 517.

¹⁷ Deutsch. med. Wchnschr., 1911, 37, p. 290.

¹⁸ Ibid., p. 638.

¹⁹ Ibid., p. 788.

²⁰ Ibid., p. 1120.

²¹ Tidsskr. f. d. norske Laegefor., 1913, 33, pp. 241, 289.

²² Amer. Jour. Med. Sc., 1908, 136, p. 226.

TECHNIC

The technic employed in the experimental production of herpes zoster was essentially that used by one of us (Rosenow²³) in connection with experiments on appendicitis, erythema nodosum, and ulcer of the stomach. The cultures were made from pus expressed from crypts and abscesses in the tonsils; from the depths of pyorrheal pockets; and from blister fluid, obtained by means of sterile pipets. The spinal fluid was obtained by aspirating it gently into a sterile glass syringe so as to avoid possible contamination from the air. Inoculations were made on blood-agar plates and blood-agar slants (the former incubated aerobically, the latter anaerobically), and into tall columns (10 to 12 cm.) of 0.2% dextrose broth, to which sterile ascites fluid and sterile tissues were usually added. The cultures for injection were incubated usually from 18 to 48 hours at 37 C., the bacteria sedimented in the containers in which they were cultivated, the supernatant clear fluid decanted, and suspensions made in salt solution so that 1 c.c. of the emulsion contained the growth from 15 c.c. of broth. In all instances, at the time of injection control cultures were made of the suspensions on blood-agar plates to prove the viability of the organisms and to be used in further study of them. The injections were usually made intravenously, but intraperitoneal and subcutaneous injections were made in some instances; they included emulsions of extirpated tonsils, mixed cultures obtained from tonsils and pyorrheal pockets, pure cultures of streptococci from the spinal fluid in herpes zoster in man, and pure cultures of streptococci obtained from the spinal fluid or from the ganglia in animals showing experimental herpes. The primary cultures from the foci, usually mixtures of streptococci and staphylococci, were often injected directly and the bacteria studied later. The animals were handled carefully, examined daily, and often caged separately, to avoid accidental lesions of the skin which might be mistaken for herpes. Herpes about the mouth, the tongue, or the eyes was easily detected, while, because of the large amount of hair, herpes of the trunk was found during life only when the lesions were marked. The lesions of the trunk were best observed on the under surface of the skin after death. Chloroform was used to kill the animals that survived the injection (60%). The examinations were made as soon after death as possible.

In order to be sure that the streptococcus in herpes was not merely an invader of the ganglia secondary to some unknown filterable virus, injections were made of the filtrates of the streptococcus cultures. Tissues for microscopic study were fixed in formalin and Zenker's fluid. The sections were stained with hematoxylin and eosin and for bacteria by the Gram-Weigert method.

REVIEW OF CASES WITH RESULTS OF CULTURES AND OF ANIMAL EXPERIMENTS

The following is a review of the clinical facts in the cases studied, the results of the cultures and of the animal experiments, and the details of representative experiments.

CASE 267

This was a case of recurring brachial herpes in a woman 45 years of age, otherwise in good health. The attacks had occurred usually in the spring and fall, following contraction of a cold but without symptoms of distinct tonsillitis.

²³ Jour. Amer. Med. Assn., 1914, 63, p. 903.

Feb. 10, 1915.—The tonsils were examined and found small, atrophic, and covered by the anterior pillars. Cultures were made from the pus expressed from pockets in the tonsils and, on February 13, practically a pure culture of a green-producing streptococcus on blood agar, short-chained in ascites dextrose broth, was obtained.

Four guinea-pigs, 3 rabbits, and 1 dog were injected; all developed herpes of the skin or of the mucous membrane of the tongue.

Rabbit 33.—Injected, Feb. 11, 1915, with the growth from 30 c.c. of ascites dextrose tissue broth.

Feb. 12.—Found dead. On removal of the skin several hemorrhagic vesicular areas were found over the left shoulder. A number of hemorrhagic vesicles were found at the juncture of the mucous membrane of the upper lip and the skin and adjacent to the lower incisor teeth. The tongue showed numerous vesicular areas, many of which were ruptured with the result that much of the mucous membrane of the tongue was absent (Fig. 16). The gasserian ganglia appeared edematous and on cross section showed small hemorrhagic areas. The 3rd and 4th left dorsal ganglia corresponding to the area of herpes over the shoulder were hemorrhagic, and there were a few small hemorrhages in the peritoneal coat of the appendix and sigmoid, 2 rather large edematous hemorrhagic areas of the mucous membrane of the stomach, and marked degeneration and acidity of the liver. There were no hemorrhages of the meninges, the brain, or the cord. The spinal fluid was slightly turbid and tinged with blood.

Feb. 13.—Blood-agar-plate cultures made from the blood and from the fluid aspirated from the hemorrhages in the skin yielded a large number of streptococci and a moderate number of staphylococci. Sections of the upper lip through the herpes area showed desquamation of epithelium and separation of cells, together with infiltration of the epidermis with red blood corpuscles and a few round cells (Fig. 17a). In the deeper layers of the hemorrhagic area (Fig. 17b) were a thrombosed blood vessel (Fig. 17c) and a rather large number of diplococci and chains, while near the surface staphylococci, also, were found. No bacteria were found in blood vessels that did not show changes, but in the thrombosed vessel a moderate number of streptococci were disclosed (Fig. 18). Also, portions of the sections that did not show changes were free from bacteria.

CASE 270

This was a typical acute thoracic herpes zoster in a woman 45 years of age. Without known cause the attack began, Feb. 9, with severe pain in the right side of the chest. The patient had once had frequent attacks of tonsillitis, but none since she had had acute rheumatic fever associated with jaundice 13 years before. For 3 months past she had lost in weight and had had a sub-acute arthritis of the right knee and symptoms suggestive of gastric ulcer.

Feb. 11.—There were marked redness and blistering over the painful area on the right side of the chest.

Feb. 12.—Her tonsils were removed.

Feb. 17.—She was free from pain and the herpetiform lesions were nearly healed. Cultures from the emulsified tonsils showed practically a pure growth of a slightly green-producing streptococcus.

The emulsion from the tonsils in NaCl solution and the cultures in ascites dextrose broth of streptococci as isolated, and after one animal passage, when

injected intravenously into 6 dogs and 10 rabbits, produced herpes in 4 dogs and 4 rabbits. After 2 passages the streptococci produced marked herpes of the tongue in 1 rabbit, while after 3 and 4 passages the streptococci failed to cause herpes in the 3 rabbits injected. Of the 4 guinea-pigs injected intraperitoneally, 1 developed herpes over the left shoulder and over the lumbar region. Three rabbits injected after the strain had been cultivated for 1 week failed to develop herpes.

Rabbit 37.—Injected, Feb. 13, with 15 c.c. of the emulsion of the tonsil in NaCl solution.

Feb. 16.—It seemed well. Chloroformed. A circumscribed vesicular eruption on the under surface of the skin of the lateral aspect of the head was found. The areas of herpes measured from 0.5 to 1 cm. in diameter, were bilaterally placed, brownish in color, and situated in the skin proper. On cross section of these areas, much fluid exuded. There was suppurative arthritis of the left shoulder-joint. There was a rather large amount of distinctly turbid blood-tinged cerebrospinal fluid.

Feb. 19.—Cultures from the blood and the right gasserian ganglion gave a pure growth of *Streptococcus viridans*; those from the shoulder-joint, *Streptococcus viridans* and hemolytic streptococci; the fluid from the vesicular areas in the skin was sterile.

Dog 217.—Feb. 13, a medium-sized white dog was injected intravenously with the growth from the original culture from the tonsil in 75 c.c. of dextrose tissue broth.

Feb. 15.—The dog seemed well, but tender over the left lower thorax. Chloroformed. On removal of the skin, a number of circumscribed areas were found showing a hemorrhagic vesicular eruption opposite the 8th and 9th ribs on the left side. On shaving the skin it was seen that only one of these had blistered (Fig. 6); the others showed only marked hyperemia on the surface of the skin. An area of localized meningitis was found in the cortex between the hemispheres. The 8th and 9th dorsal spinal ganglia on the left side did not show hemorrhages on the surface, but on cross section showed distinct areas of hemorrhage. The joint fluid was turbid.

Feb. 16.—Cultures from the blood and from the edematous fluid in the vesicles and in the joint were found sterile. Sections of the 8th dorsal ganglion showed marked congestion, irregular staining of the ganglion cells, hemorrhage, especially in the sheath, round-cell infiltration (Fig. 7a), and thrombosis of the accompanying artery (Fig. 7b). The 9th dorsal ganglion showed similar changes, including a thrombosis of its vein. Altogether, 14 gram-positive diplococci were found in these ganglia. Serial longitudinal sections of the 8th and 9th dorsal ganglia and of the accompanying nerve roots showed that the thrombosed vessels were the artery and the vein supplying them. Cross-sections of the cord at the level corresponding to the 8th dorsal vertebra showed areas of hemorrhage in the gray matter in the posterior columns. The nerve cells surrounding the hemorrhage stained irregularly, and under high power considerable blood pigment was found. The blood vessel accompanying the posterior root just at the exit of the nerve fibers from the cord and beneath the dura was almost completely plugged by polymorphonuclear leukocytes and other cells (Fig. 8). Prolonged search resulted in the finding of 4 diplococci: 1 free in the vessel, 2 within leukocytes, and 1 in the wall of the vessel on the side of the nerve. Sections at two slightly different levels showed hemorrhages in the posterior nerve root and a thrombosed blood vessel under the dura directly opposite the posterior root.

CASE 276

This was a severe unilateral herpes zoster involving the left thoracic region, of 4 days' duration, in a laborer 49 years of age. The blistering was marked, the pain intense. The patient thought he had had high fever at the onset of the disease, but with the appearance of the eruption it had disappeared. He had never had a similar attack. The man was poorly nourished, seemed ill, coughed and raised small amounts of sputum, but the lungs were sterile.

Feb. 22.—The tonsils were found cryptic and the teeth surrounded by marked gingivitis. Cultures were made from the pus expressed from the tonsils, from the material drawn into a pipet from the inflamed gums, and from sputum, spinal fluid, blister fluid, and blood. The spinal fluid was clear, but smears from the sediment showed a moderate number of mononuclear cells in which there were a few diplococci.

Feb. 23.—Cultures from the blood were sterile; the spinal fluid gave a pure culture of a short-chained streptococcus and a few colonies of streptococci in ascites dextrose agar. Cultures from the tonsils, the teeth, and the sputum revealed chiefly green-producing colonies of streptococci, *Micrococcus catarrhalis*, and staphylococci. Cultures from the clear blister fluid remained sterile; those from the bloody blister fluid gave a few chains of diplococci, a spore-forming bacillus, and staphylococci.

The original cultures from the tonsils, from pus pockets about the teeth, and from sputum in ascites dextrose broth were injected intraperitoneally into 1 guinea-pig each, all 3 developing herpes. Intravenous injections of cultures of the streptococcus from each of these into 1 dog, 1 rabbit, and 1 guinea-pig each, were followed by herpes in all but 1 dog and 1 rabbit. The pure culture of the streptococcus from the spinal fluid of these animals caused herpes in 2 rabbits and 1 dog. After cultivation from 1 to 2 weeks, this streptococcus, when injected into 5 rabbits and 2 dogs, failed to produce herpes. The streptococcus from the spinal fluid (second culture) produced herpes of the eye and the lip and hemorrhage in the corresponding ganglion in a dog.

Rabbit 46.—Feb. 23, injected intravenously with the growth of a pure culture of *Streptococcus viridans* from the infected gums in 60 c.c. of ascites dextrose tissue broth.

Feb. 24.—Chloroformed. Marked herpes of the tongue (Fig. 13), marked areas of localized edema in the lung and the mucous membrane of the trachea suggestive of herpes were found. There were a moderate number of localized hemorrhages and edema of the mucous membrane of the stomach with 1 ulcer near the lesser curvature and 1 in the fundus. There was a moderate turbidity of the joint fluid from both knees. The spinal fluid was slightly blood-tinged. The gasserian ganglia appeared edematous, but no distinct hemorrhages could be made out.

Feb. 26.—The blood, the spinal fluid, the gasserian ganglia and the joint fluid yielded a large number of green-producing streptococci, and plate cultures from the ulcer in the cardiac end of the stomach gave 500 colonies of streptococci. Sections of the ganglia of the vagus nerve showed 1 rather large hemorrhage between the cell groups, and Gram-Weigert stains showed a few diplococci in the hemorrhagic area. Sections through the ulcerated area at the tip of the tongue showed desquamation, infiltration, and necrosis of the epithelium (Fig. 14b), slight round-cell infiltration of the underlying

muscle (Fig. 14a), and an aggregation of leukocytes in a small adjacent blood vessel (Fig. 14c). Stains for bacteria revealed a large number of gram-staining diplococci covering the ulcerated area (Fig. 15).

Dog 222.—Medium-sized brown and white dog, injected, Feb. 23, intravenously with the growth from 90 c.c. of an ascites-dextrose-broth culture from the tonsil.

Feb. 25.—It seemed well. Chloroformed. Marked hemorrhage and edema were found in the very lowest portion of the esophagus and the first portion of the stomach. This did not have the appearance of the usual hemorrhages, and the blood was unquestionably diluted with serous fluid. A number of herpetiform lesions could be found under the pleura in the left lung on the upper surface of the lower lobe. The largest of these measured 0.5 by 4 cm. (Fig. 23a). The contents of these areas consisted of hemorrhagic edematous fluid. The sympathetic and the vagus ganglia on the right side were imbedded in an area of hemorrhage; the spinal fluid was distinctly turbid; no lesions could be found in the spinal ganglia. The liver showed marked congestion; the joint fluids were clear.

Feb. 26.—Cultures from the blood, the joint fluid, the spinal fluid, the bile, and from the edematous fluid from the herpetiform lesions in the lung were sterile. Sections of the spinal cord, the spinal, the sympathetic, and the vagus nerves, and of a number of spinal ganglia, corresponding to the segment of the lesion of the stomach, showed no changes. The vagus and the sympathetic ganglia showed no gross lesions within their substance, but the capsules and the surrounding areolar tissue were hemorrhagic. The accompanying blood vessel of the sympathetic ganglion showed a beginning thrombosis; the thrombus filled one-half the lumen of the vessel and consisted chiefly of polymorphonuclear leukocytes and large mononuclear cells. Gram-Weigert stains showed diplococci in the hemorrhagic area and a few within the thrombus. A section of the herpes-like area in the lung showed dilatation of capillaries, hemorrhage and edema into alveoli, but little leukocytic infiltration (Fig. 24).

Rabbit 47.—Injected intravenously, Feb. 23, with the growth from 25 c.c. of an ascites-dextrose-broth culture from the sputum.

Feb. 24.—Found dead. Numerous small punctate hemorrhages were found in the skin of both ears, some of these distinctly vesicular in character. A ruptured vesicle was found near the inner angle of the right eye and near the juncture of the cornea. The left eye was normal except for some hemorrhages and edema, especially over the lower lid. A number of these had ruptured and glued together the margins of the lids. On the upper left lid a distinct vesicle in the subcutaneous tissue was found. There were a few lesions in the fascia covering the subscapular muscles on the right side. The spinal cord and the ganglia showed no apparent change. The gasserian ganglia appeared edematous. The middle ears showed a marked exudation; and there was infiltration of pus along the auricular branches of the 5th nerve as they passed along the anterior upper aspect of the temporal bone. Fluid from the knee joints was turbid, smears revealing leukocytes and diplococci.

Feb. 26.—A large number of green-producing streptococci in pure culture were obtained from the blood, the spinal fluid, and the gasserian ganglia. Sections of the left gasserian ganglion showed small areas of hemorrhage and round-cell infiltration, which was most marked in an area at the juncture between the nerve and the ganglion. The infiltration extended along the nerve

sheath for a considerable distance (Fig. 9a). A rather large number of diplococci were found in the infiltrated areas, but not in the normal portion (Fig. 10). Sections of the spinal cord showed no changes, but the left spinal ganglion at a level corresponding to the lesions found in the shoulder showed slight leukocytic infiltration and small hemorrhages.

Fig 59.—A medium-sized white and black guinea-pig was injected intraperitoneally, Feb. 23, with the growth from 15 c.c. of an ascites-dextrose-broth culture from the sputum.

Feb. 24.—Very ill. Chloroformed. Herpes of the upper lip and inner nostrils was seen only from the under surface of the skin. There were serofibrinous peritonitis and pleuritis; marked hemorrhages of the stomach; marked degeneration and acidity of the liver. There were no gross lesions of the gasserian ganglia, but sections showed areas of hemorrhage, in which were found a number of diplococci. No diplococci could be found in the more normal portion.

Dog 221.—Medium-sized fox terrier, injected, Feb. 23, with the growth from 90 c.c. of an ascites-dextrose-tissue-broth culture from the sputum.

Feb. 25.—Lame in the left hind leg. Chloroformed. There was one herpetiform lesion in the subcutaneous fat over the left shoulder blade and the fluid from the left knee was turbid. There were no other gross findings except a large amount of the usual turbid spinal fluid.

Feb. 26.—Cultures from the joint fluids and from the blood and the spinal fluids were sterile. Sections of the cord showed no hemorrhages. The ganglia and the associated nerve roots showed areas of round-cell infiltration, in which a few diplococci were found.

CASE 278

This was a typical severe thoracic herpes zoster in a robust laborer 44 years of age. The area involved showed numerous small and large blisters. It was supplied by the left 7th and 8th intercostal nerves and extended from the median line in the back to the median line in front. The pain, which had begun 3 days before, was still severe; blistering had occurred 1 day before. The patient had been well for years except for an attack of sciatica 9 months before. Cultures were made from the small amount of pus expressed from the chronically infected tonsils and from the pus aspirated from the depth of several pyorrheal pockets and from the blister fluid.

Feb. 23.—Cultures on blood-agar plates from the tonsils and pyorrheal pockets yielded chiefly *Streptococcus viridans*, a few colonies of hemolytic streptococci, and a moderate number of staphylococci. The cultures from the blister fluid were sterile. Smears from the cultures in ascites dextrose broth showed very long chains and clumps of streptococci, larger short-chained diplococci resembling pneumococci, and staphylococci.

March 12.—The patient was examined again and cultures made exactly as before. He had been entirely free from pain for 10 days and feeling as well as ever.

The cultures from the teeth, when injected into 1 rabbit, failed to produce herpes. The original culture from the tonsils, containing both staphylococci and streptococci, produced herpes in 2 out of 3 rabbits and in 1 dog. The mixed culture of streptococci and staphylococci obtained from the spinal fluid of the dog showing herpes, produced herpes in 2 dogs and 1

rabbit. The filtrate (proved to be sterile) from the broth culture from the tonsil, did not cause herpes in the 2 rabbits injected. The culture obtained from the tonsil on March 12 after recovery, injected into 3 rabbits, developed herpes in 1.

Dog 225.—A large brown and white dog, injected intravenously, Feb. 24, with the growth from 90 c.c. of an ascites-dextrose-broth culture from the tonsil.

Feb. 25.—It seemed ill and in pain. Slight pressure over the lower thorax caused the animal to yelp. There were no visible changes of the skin, and no herpes about the mouth or the eyes.

Feb. 26.—The dog seemed somewhat better than it had been the day before. No herpes could be made out, but the skin over the right lower thorax was distinctly hyperemic.

Feb. 27.—At 9 a. m., the dog was very sensitive over the thorax. There were 2 large bluish-red edematous areas, approximately 5 by 8 cm., in the skin over the lateral and lower aspects of the thorax. Slight pressure here caused the dog to yelp. The pain seemed to be especially severe at intervals of from 10 to 30 minutes; at such times it cried out and rolled from side to side as if in great pain. The animal was alert mentally and when petted or spoken to kindly, wagged its tail. The condition grew worse, breathing labored. A number of blisters appeared over the area described. The animal was then chloroformed and examined at once. The skin over the lower and anterior portion of the thorax on both sides showed marked hemorrhage, edema, swelling, and blistering over areas approximately 6 by 10 cm., the long axis being parallel with the ribs. These were surrounded by numerous smaller herpetic lesions (Fig. 11), some of which did not involve the thick hair-covered overlying epidermis. The edema and infiltration of the large areas extended through the wall of the chest over a small area (3 cm.) on both sides where the peritoneum was blistered. All gradations in the character of the fluid in the lesions, from a clear serous fluid to a deeply blood-tinged and bloody purulent fluid, were found. The larger areas appeared infected. It was impossible to shave away the hair over these areas without causing the blisters to rupture. Herpetiform lesions were also found over the lower portion of the abdomen and of the prepuce, and under the right shoulder blade. The peritoneal cavity contained a moderate amount of turbid fluid. The stomach, in extreme spasm, contained no food but a moderate amount of bloody mucus, which reacted faintly acid to litmus. The mucous membrane of the fundus and of the pyloric end of the stomach showed edematous raised and opaque areas, in which were found many small hemorrhages and a number of superficial erosions. These areas had the typical appearance of herpetiform lesions. The liver showed marked congestion and mottling. The wall of the gall-bladder contained 4 circumscribed edematous hemorrhagic areas, resembling herpes. The kidneys appeared normal except for several circumscribed opaque edematous areas resembling infarcts. The lungs appeared normal except that there were altogether 7 subpleural circumscribed elevated collections of bloody serum having the appearance of vesicles. The myocardium was opaque and showed a number of small infarcts (2 by 5 mm.). The left auricle contained 2 herpetiform lesions at the juncture of the auricular appendix and the main body of the auricle. One of these appeared to involve the sinu-auricular node. The spinal ganglia in the lower cervical and upper dorsal region especially on the right side were imbedded in dark clotted blood. The hemorrhagic areas here were often fused, giving the appearance of an acute

diffuse pachyleptomeningitis. Similar but smaller hemorrhages were found around the ganglia and the cord in the lumbar region. The vagus and the right sympathetic ganglia were surrounded by small hemorrhages and appeared edematous. The brain, vagus and sympathetic nerves, the thyroid, adrenals, pancreas, the mucous membrane of the mouth, eye, and esophagus, the spleen, testicles, and the extremities appeared normal.

Feb. 28.—Cultures made from the brain substance, from the herpetiform lesions in the gall-bladder and the lung, from the bile and the joint fluid were sterile. The cultures from an infarct in the myocardium, from the blood, and from two subcutaneous lesions showed *Staphylococcus aureus* only. The more marked lesions in the skin showed staphylococci, a large bacillus, and streptococci. The peritoneal and spinal fluids yielded staphylococci and streptococci. Ascites dextrose agar-plate cultures of the emulsified tissue of two of the herpes-like areas in the stomach gave 30 and 50 colonies of streptococci. A section of the involved skin showed edema, leukocytic infiltration, and hemorrhage, especially of the deeper layers. The squamous epithelium in portions was raised, desquamated, and in some areas sloughed away (Fig. 12). The deeper cuboidal cells were everywhere intact. Gram stains showed clumps of cocci in diplococci and short chains, and a few bacilli in areas showing leukocytic infiltration. In the intercostal and abdominal muscles from the involved area were marked interstitial infiltration and hemorrhage. The spinal ganglia and the posterior nerve roots corresponding to the areas of herpes of the thorax were surrounded by marked hemorrhages and leukocytic infiltration, which extended into the sheath. The associated blood vessels showed partial thrombosis. A moderate number of diplococci and a few round single and clumped cocci were found in the hemorrhagic area showing blood pigment. Longitudinal sections of the subcutaneous nerves running into the involved area disclosed no changes except infiltration of the sheath in the involved area. Proximal to this point there were no changes. The vagus ganglion was surrounded by hemorrhages and leukocytic infiltration, chiefly of the capsule of the ganglion and the nerve sheath for a short distance (Fig. 25). Diplococci were found in the hemorrhagic area. The sympathetic ganglion showed no changes except slight hemorrhage beneath its sheath. The vagus and the sympathetic nerves remote from the ganglia showed no changes. The areas resembling herpes under the pleura in sections showed extravasation of blood into the distended alveoli. The blood corpuscles in the alveoli were separated and did not fill them completely.

CASE 281

This was a case of recurring herpes zoster involving the upper and outer aspects of the right thigh in a nervous woman 40 years of age. The attacks had occurred yearly during early spring, and usually were not associated with distinct tonsillitis or other apparent infection. Three years before, she had had a severe attack of bilateral thoracic herpes zoster, and since then had had more or less distress after meals suggesting duodenal ulcer. The attack here described began 10 days after the onset of a typical attack of diphtheria. Seven days after the temperature had become normal (2 days before the attacks described) and after the throat cultures had failed to show diphtheria bacilli, the patient began to have pain in the outer aspect of the thigh, followed by redness and blistering on the third day after the appearance of pain.

Feb. 25.—The tonsils were small but red; from the crypts was expressed a small amount of fluid pus. Cultures were made from this pus and from the blister fluid.

Feb. 26.—Blood-agar-plate cultures gave a large number of green colonies of streptococci and of *Micrococcus catarrhalis*. Loeffler's serum slants yielded no diphtheria bacilli. Smears from the ascites-dextrose-tissue-broth cultures showed pure culture of a short-chained streptococcus. The cultures from the blister fluid were negative.

March 3.—The patient had fully recovered, pain was absent, the blistered areas nearly healed. Cultures were again made from the tonsils.

March 4.—Blood-agar plates inoculated with material from the tonsils showed, as before, many green colonies of streptococci, a few colonies of hemolytic streptococci, and of *Micrococcus catarrhalis*, but smears from the broth cultures showed much longer chains of streptococci than those in the former culture.

The primary culture from the tonsil pus during the attack was injected into 2 dogs and 2 rabbits. Only 1 rabbit developed herpes. The culture of the streptococcus obtained pure from the spinal fluid of this rabbit was injected into 6 rabbits and 1 dog, of which 4 rabbits developed herpes, the result in the dog being negative. The filtrate of the broth culture, thought to be sterile, but from which a few streptococci were isolated later, produced herpes of the right lower abdomen and of the outer aspect of the right thigh, associated with hemorrhage of the corresponding ganglion in the one rabbit which was injected (Rabbit 56, Case 281), and herpes of the upper lip in 1 of 2 dogs previously injected with the growth from the tonsil. A portion of this filtrate was then refiltered and again injected intravenously into a rabbit of the same size; no herpes developed and cultures made from the sediment of a centrifugated portion remained sterile. The cultures made after the patient had recovered failed to produce herpes in the one rabbit injected.

Rabbit 62.—Injected intravenously, Feb. 26, 1915, with the growth from 45 c.c. of an ascites-dextrose-tissue-broth culture from the tonsil.

Feb. 28.—The rabbit seemed ill and in pain. There was a marked herpes of the skin of both ears. Chloroformed. The skin of both ears was studded with numerous small hemorrhages and vesicular areas (1 to 7 mm. in diameter). These bore no relation to the site of the injection. A number of the vesicular areas had ruptured, and the dried serum covered the area. On cross section of a number of these a relatively large amount of sero-sanguineous fluid exuded. There was herpes of the skin over the upper aspect of the thighs (more marked over the right) and over the lower abdomen (Fig. 2). The herpes followed the distribution of the cutaneous nerves. The mucous membrane of the tongue was edematous at points, and a few ruptured blisters were found along the margin. The duodenum showed 4 edematous hemorrhagic areas 1 cm. beyond the pyloric ring. Three of these were distinctly vesicular, while the fourth was a small submucous fading hemorrhage. The gall-bladder wall contained 6 small whitish edematous areas over the fundus. The kidneys were pale and presented a peculiar appearance (Fig. 20). The capsule was raised in areas by clear fluid, which escaped on section. When the capsule was stripped, much fluid exuded, and some of the edematous opaque areas were found to extend into the cortex for a considerable distance. The cut surface was very moist. The medulla was grayish-red. The mucous membrane of the pelvis was edematous and blistered in areas. The mucous membrane of the ureters and the bladder showed no changes. The pericardial sac contained a moderate amount of turbid fluid; the parietal layer was edematous. The myocardium was mottled grayish-red; the endocardium was normal. The lungs showed a peculiar mottled appearance, but no distinct vesicles

could be found. The right gasserian ganglion was edematous. The right auriculo-temporal nerve was surrounded by pus. The drum-membrane and the lining of the middle ear on this side were edematous and hemorrhagic, and the cavity contained a thin pus in which a number of diplococci were found. The left gasserian ganglion and the middle ear presented a similar appearance. The meninges were dry; the brain and the cervical and dorsal ganglia appeared normal. In the lumbar region extradural hemorrhages surrounded the posterior nerve roots and ganglia. No gross hemorrhages could be made out on the freshly cut surface of the ganglia and cord. The sympathetic ganglion on the right side and the vagus ganglion on the left side were surrounded by hemorrhages. Those on the opposite sides showed less change. Diplococci, showing disintegration, were found in the hemorrhagic area surrounding the left vagus ganglion (Fig. 22). Stomach, liver, pancreas, spleen, lymph glands, eyes, thyroid, and joints were normal.

March 1.—Cultures from spinal fluid, gasserian ganglion, pericardial fluid, kidney, and blood yielded short-chained green-producing streptococci only. Sections of the cord, of the nerve roots, and of the ganglia corresponding to the area of herpes showed slight round-cell infiltration and hemorrhages of the posterior horn, of the corresponding ganglia and the associated sheaths, and thrombosis of the accompanying vessels (Fig. 3). Diplococci here were easily found. Sections of a herpetiform lesion of the skin of the ear showed sloughing of the epidermis, round-cell and red-blood-cell infiltration and a few diplococci in the cutis vera.

Sections of kidney stained by hematoxylin and eosin exhibited circumscribed areas of edema. The parenchymatous cells of the tubules were swollen; the protoplasm was granular and vacuolated; the nuclei stained poorly, some retaining their form, others showing disintegration. Some of the glomeruli in these areas were distended, the cells separated and the spaces filled with a finely granular fluid. The adjacent areas appeared normal except for congestion of the blood vessels, small hemorrhages, and compression of the tubules and the glomeruli. These areas extended well through the cortex. The contrast between the edematous cells with poorly stained nuclei and the intermediate portion of compressed well-stained cells was striking. The medullary portion was normal except for marked congestion of the blood vessels (Fig. 21). Stains for bacteria showed many diplococci, which were found, in radiating lines, chiefly between and within the cells of the convoluted tubules of the areas showing the herpes, the more normal portions and glomeruli disclosing no bacteria.

Rabbit 56.—A large white Belgian hare injected intravenously, March 2 and 3, 1915, with 10 and 5 c.c. of the filtrate of the streptococcus culture in ascites dextrose tissue broth from the spinal fluid of Rabbit 62.

March 6.—It seemed well. Chloroformed. No gross lesions were found except several areas of herpes, 0.5 to 1 cm. in diameter, of the deeper layer of the skin over the left lower abdomen and over the upper and outer aspect of the right thigh. A thorough search for lesions of the corresponding spinal ganglia failed to show gross lesions, but they were saved for microscopic sections.

March 8.—Blood, spinal fluid, and lung were sterile. Sections of the spinal ganglia, the nerve roots, and the pia-arachnoid membrane showed distinct hemorrhages and round-cell infiltration. The associated larger vessels were surrounded by leukocytic infiltration. Gram-Weigert stains showed diplococci in the infiltrated areas.

CASE 368

This was a case of lobar pneumonia with marked herpes of the lips, the nostrils, and of the left side of the face in a young man.

March 22.—The 5th day of the disease cultures were made from the tonsils and from the sputum.

March 23.—Cultures from the tonsils and from the washed sputum gave a large number of green-producing colonies resembling pneumococci. The former yielded also hemolytic streptococci and *Micrococcus catarrhalis*. The broth culture gave chains of diplococci.

The culture from the sputum in ascites dextrose broth was injected into 1 dog and 1 rabbit. The former developed herpes of the lip and the tongue; the latter of the left side of the face and head and a bronchopneumonia 48 hours after the injection. The culture from the tonsil was also injected into 1 dog and 1 rabbit. The former developed herpes of the lip; the latter, herpes of the conjunctiva of the left eye, and of the skin over the left side of the face and the thorax. The gasserian ganglion of the dog injected with the tonsil strain showed areas of hemorrhage (Fig. 19a) and round-cell infiltration (Fig. 19b). The cultures of the strain isolated from the spinal fluid of the rabbits injected with strains from sputum and tonsil failed to ferment inulin, but otherwise closely resembled pneumococci.

CASE 382

This was an acute gangrenous thoracic herpes zoster in a man 56 years of age. Beginning March 30, 1915, the patient had pain in the right lower costal nerve for a week. The day before, a rash had appeared over the tender areas and during the night a number of small blisters had appeared. There was no other complaint, except nasal catarrh, for a year past. Leukocytes numbered 10,000; hemoglobin 90%. The tonsils were small, cryptic, and covered by the anterior pillars. By making pressure outside the left tonsil a small-sized abscess was ruptured. Cultures were made from the pus obtained.

April 2.—Cultures on blood-agar plates yielded chiefly *Streptococcus viridans*, a few hemolytic streptococci, and staphylococci.

Injection of the growth in an ascites-dextrose-broth culture from the tonsil into 2 rabbits, produced in one herpes of the left margin of the tongue, marked herpes of the conjunctiva of the right eye, moderate of the left, and herpes of the left side of the thorax; in the other, herpes of the lateral aspect of the abdomen. The pure culture of streptococci obtained from the spinal fluid of these rabbits produced herpes in 2 of 4 rabbits injected; in one of the left thorax; in the other, of the lip, the tongue, and the left side of the face.

During the night following the examination the symptoms became much worse, and on April 7, Dr. Kretchmer, who kindly referred the patient to us, reported that the patient was suffering excruciating pain and that there were numerous ulcers at the site of the lesions. It would seem that, during the examination or later, there had occurred a new invasion of the bacteria which were proved to have affinity for the posterior ganglia, converting a mild attack into a severe one.

CASE 391

This case was one of acute herpes zoster in a man 43 years of age. Forty-eight hours after taking 5 grains of calomel, which was thought to have salivated him, the herpes began in the left lower lip, then spread to the left side of the tongue, to the left buccal surface, and thence to the left side of the

face, including the left ear. The pain was intense for several days before the eruption appeared, also throughout the attack and afterward—4 weeks in all—altho the herpes had healed. There were marked swelling and edema of the involved areas, especially of the ear, resembling erysipelas. This was thought to be a secondary infection due to the streptococcus, and antistreptococcus serum was given. A marked neurasthenic state developed after the herpes began. The man had had pyorrhea for years.

April 16.—The tonsils were found to be small, but hyperemic and visibly infected. There was pyorrhea, especially about the lower incisors. Cultures were made from the small amount of pus expressed from both tonsils and from that aspirated from the pyorrheal pockets.

April 20.—Blood-agar plates made from the cultures in ascites dextrose broth inoculated with the pus from the tonsils and from the teeth, showed *Streptococcus viridans*, *Staphylococcus*, and a few colonies of *Bacillus influenzae*.

The original culture in ascites dextrose broth from the pyorrheal pocket was injected intravenously into 2 rabbits and 1 dog. One rabbit and the dog developed herpes. In the rabbit, the herpes was situated under the eye and the left lateral thorax; in the dog, in the right upper lip and the tongue. The culture from the tonsil was also injected into 2 rabbits and 1 dog; of these, only 1 rabbit developed herpes, the skin over the right hip being involved. The relatively high incidence of herpes following these injections is in keeping with the fact that, while the acute symptoms had subsided, the pain was still present when the cultures were made.

Completely negative results were obtained following intravenous injection of the cultures from the tonsils in a case of recurrent herpes of the mouth, and with the cultures obtained from the nasal discharge in a patient suffering from acute rhinitis associated with simple herpes of the lip.

RESULTS OF THE CULTURES

Cultures were made in 11 cases of herpes. Of these 5 were marked thoracic herpes zoster; 1 was severe herpes of the left side of the face and the left ear; 3 were recurring (1 involving the left arm, 1 the outer and upper aspect of the right thigh, and 1 the mucous membrane of the mouth); 1 was a marked herpes of the lips and of the left side of the cheek during pneumonia; and 1, a mild herpes of the lip during an attack of acute rhinitis. In no instance was there acute tonsillitis. The pus pockets found in the tonsils were small. All but 4 patients had pyorrhea. The patients included 1 woman 45 years old, 9 men from 40 to 56 years old, and 1 young man. The cultures from the tonsils (all of which contained pus), from the sputum, and from the pyorrheal pockets yielded a preponderance of moist green-producing colonies of a non-encapsulated, gram-staining, short-chained, often lanceolate, streptococcus. The cultures from the clear blister fluid in human herpes were usually sterile, or showed a few colonies of a large staphylococcus; but in one patient (Case 276) cultures from a hemorrhagic blister fluid showed a few colonies of a green-producing streptococcus, of a large gram-staining spore-forming bacillus, and of staphylococci.

Cultures from the spinal fluid and the blood were made in only one case. The former gave a pure culture of the streptococcus; the latter remained sterile. The fermentative powers of 7 of these strains that were proved to have affinity for the ganglia were tested on various sugars in broth. All but 1 produced acid in saccharose; all but 2 in salicin; 3 fermented raffinose, and 2 mannite; none fermented inulin. In short, these streptococci had the features of a pneumococcus, except high virulence, capsule, and inulin-fermentative powers (Fig. 26). At times there were found in the tonsils and pyorrheal pockets a few hemolyzing colonies of streptococci and frequently small dry slightly green-producing colonies of a smaller streptococcus. This was true both in blood-agar plates made directly and in those from the ascites-dextrose-broth cultures. *Micrococcus catarrhalis* was commonly present in the usual numbers. The cultures differed from those from the tonsils in other diseases in that they showed an unusually large number of staphylococci. Anaerobic cultures on blood agar were not characteristic.

RESULTS OF INTRAVENOUS INJECTIONS

In Table 1 is given a summary of the results of the injection of the strains (1) when first isolated, (2) after cultivation for a time, and (3) after animal passage. Sixty-one animals were injected with 11 strains as isolated. Of these, 70% developed herpes of the skin (Figs. 1, 2, 6, and 11); 15% herpes of the eyelids—a total average of experimental herpes in 75%. The lesions varied from those very small, just recognizable, to others very large and marked (Dog 225).

TABLE 1
LOCALIZATION OF STREPTOCOCCI FROM HERPES ZOSTER

Time of Injection of Streptococci	Strains	Animals Injected	Percentage of Animals Showing Lesions in				
			Appendix	Stomach	Duodenum	Gall-bladder	Pancreas
				Hemorrhage	Ulcer		
When isolated.....	11	61	10	29	8	16	2
Later.....	6	15	0	13	7	7	13
After animal passage.....	4	7	0	28	10	0	0

In some instances the tendency of the strains from the apparent atria of infection to produce herpes was so marked that it occurred in nearly all animals injected intravenously, and in some it developed even after intraperitoneal injection. Thus, in one instance (Case 276) the

original cultures in ascites dextrose broth from the spinal fluid produced herpes in guinea-pig, rabbit, and dog. The pure cultures of the streptococcus from the spinal fluid of these animals produced herpes in 2 rabbits and 1 dog. That the herpes is due to the streptococci injected and not to an ultramicroscopic organism is indicated by the fact that sterile filtrates of these cultures failed to produce the disease. Moreover, when the characteristic affinity was marked, only a few streptococci were necessary to produce the disease. Thus, in one rabbit herpes of the skin with lesions and streptococci in the corresponding spinal ganglion (Case 281, Rabbit 56) followed injection of what was thought to be a sterile filtrate, but which later by centrifugation and cultures from the sediment was proved to contain a few living streptococci (probably not more than 10). A portion of the filtrate was again filtered and injected. It was now proved to be free from streptococci for, accordingly, it failed to produce herpes. Injection of the emulsion of the extirpated tonsil in NaCl solution at the outset of an attack (Case 270, Rabbit 37), as well as of the original cultures in broth containing a mixture of bacteria, was followed by a herpes that was proved to be due to streptococci.

The lesions were usually unilateral, especially after the injection of small doses, altho after the injection of large doses bilateral herpes occurred rather often. In some instances the location of the herpes in the animals corresponded rather closely to that in the patients from whom the cultures had been obtained (Case 281, Rabbits 62 and 56; Case 368, Dog 299).

TABLE 1—*Continued*
LOCALIZATION OF STREPTOCOCCI FROM HERPES ZOSTER

Percentage of Animals Showing Lesions in											
Intestines	Joints	Endocardium	Pericardium	Myocardium	Muscles	Kidneys	Lungs	Skin	Tongue	Eyes	Parotids
8	11	5	11	5	11	5	21	70	15	15	0
7	60	7	0	20	40	7	20	7	0	13	0
0	43	0	14	0	28	0	43	28	14	0	0

Table 1 shows further that after the streptococci are cultivated on artificial media (7 to 14 days) and after animal passage (2 to 5) they largely lose the power to produce herpes; it occurs in only 7 and 28% of the animals injected. Likewise, the cultures made from the pre-

sumable infection-atrium 7 to 10 days after recovery, produced herpes in only 1 of 9 rabbits and 3 dogs which had been injected. The patient (Case 391), however, who continued to have severe pain (post-herpetic neuralgia) 4 weeks after the lesions of the skin had healed, still harbored streptococci, which produced herpes in most of the animals injected.

The posterior roots or ganglia corresponding to the area of herpes of the skin (Figs. 1, 2, 6, and 11) nearly always showed hemorrhages and edema. Smaller hemorrhages were usually found about the neighboring ganglia in those animals with severe herpes, tho the corresponding area of the skin was free from herpes. The hemorrhage at times extended for a short distance along the sheath of the spinal nerve, but the intercostal nerves and the cutaneous branches remote from the lesions in the ganglia and the skin showed no gross or microscopic changes. The hemorrhages about the ganglia and the posterior root at times extended into the loose connective tissue of the external and posterior portion of the dura, presenting the picture of an external pachymeningitis. Herpes of the skin of the ears of rabbits, when present, was usually bilateral, and was nearly always accompanied by herpes of the tongue. In two rabbits with marked herpes of the external ears there were found what appeared to be herpes of the drum and middle ear and an infection extending from the gasserian ganglia along the auricular nerve. Herpes of the face, the eyelids, and the tongue was usually accompanied by hemorrhage of the gasserian ganglion.

Herpes of the viscera occurred chiefly after injection of large doses in animals showing marked bilateral herpes of the skin. In some instances, however, it occurred without herpes elsewhere (Case 276, Dog 222). Herpes has been observed of the lung and the pleura (Fig. 23), of the peritoneum, the gall-bladder, the mucous membrane of the stomach and duodenum, of the kidney (Fig. 20), and of the visceral pericardium. Herpes of the viscera was always accompanied by hemorrhage and edema about the ganglia of the vagus or the sympathetic nerve, or both. Lesions here were not found where visceral herpes was absent.

Cultures made in the case of animals after injection showed that the streptococci tended to disappear from the blood. Sixty percent of the animals survived the injection. This afforded opportunity to study the rôle played by the bacteria in the production of the disease. Routine cultures were made from the spinal fluid, the hemorrhagic area about

the ganglia, the blood, the blister fluid, and the joint fluid in the animals. The spinal fluid showed a characteristic turbidity, which was due chiefly to mononuclear cells. The cultures from the spinal fluid and from the hemorrhagic ganglia nearly always showed a larger or smaller number of colonies of the characteristic streptococcus, even when the blood and other cultures were sterile. In fact, this was common after injections of the primary cultures from the focus, containing in addition to streptococci, staphylococci. The streptococci from the spinal fluid in these animals showed a marked tendency to produce herpes when injected the second time, but in subsequent injections rarely produced herpes. Cultures from the herpetiform lesions in the skin, which showed no hemorrhage, and from animals that survived the injection, were usually sterile; while from the marked lesions showing hemorrhage and at times necrosis and beginning gangrene (Case 278, Dog 225), the organism injected, together with staphylococci and bacilli, was usually obtained. Localized meningitis was observed once. The occurrence of lesions in the other organs corresponds closely to the average incidence of lesions in these organs following the injection of streptococci from a wide range of sources.²³

MICROSCOPIC ANATOMY OF THE LESIONS

Microscopic examinations of the milder herpetic areas in the skin showed separation of the cells, desquamation, and, usually, slight round-cell infiltration. Bacteria were not found in these. The marked lesions (Fig. 12) showed desquamation of the epithelium of the epidermis, hemorrhage, marked leukocytic infiltration, and at times thrombosed blood vessels (Fig. 17c). In these, staphylococci, streptococci, and bacilli were found. The sections in herpes of the tongue and the lip showed sloughing of the mucous membrane, partial or complete thrombosis of blood vessels, marked hemorrhage of the muscular layer, and leukocytic infiltration (Fig. 17). The blistered epithelium of the tongue sloughed promptly, and the ulcerated base revealed a large number of streptococci in all of the sections examined (Figs. 14 and 15). The lesions in the ganglia and in the adjacent nerve trunks consisted usually of small areas of hemorrhage and round-cell infiltration immediately surrounding the capsule of the ganglia or the associated nerve-sheath and around the accompanying blood vessels (Figs. 3, 5, 7, 8, 9, 19, and 25). The blood vessels of the ganglia and the posterior root

²³ Jour. Amer. Med. Assn., 1915, 65, p. 1687.

usually showed partial or complete thrombosis (Figs. 3, 7, and 8), the thrombi consisting of polymorphonuclear leukocytes and large mononuclear cells and fibrin (Fig. 8).

Serial sections in one instance showed that the thrombus in the artery to the ganglion extended for a considerable distance along the posterior root and under the dura. Diplococci, often in large numbers, were found in the hemorrhagic and infiltrated areas of the spinal, vagus, and sympathetic ganglia, but not in the portions free from changes or in the normal ganglia (Figs. 5, 10, and 22). The bacteria have been found in the thrombosed blood vessels accompanying the lesions of the ganglia and posterior horns and in the peripheral lesions in the herpes of the lip and the tongue (Figs. 4 and 18). It must not be supposed that the finding of diplococci in the hemorrhagic infiltrated areas about the ganglia was a part of the general invasion, because they were absent in the portions of sections showing no change and present, in many instances, in the lesions in animals seemingly well, with blood sterile. Longitudinal sections of the vagus, sympathetic, intercostal, and cutaneous nerves and of the accompanying sheaths remote from the lesions in the ganglia or skin showed no changes or bacteria. Sections of the spinal cord in a few instances showed hemorrhage and round-cell infiltration in the posterior columns.

SUMMARY AND GENERAL DISCUSSION

The streptococcus found by us, which has such marked affinity for the posterior root ganglia, resembles morphologically the diplococci found in the gasserian ganglia by Sunde.¹³ The cells found in the spinal fluid in the animals injected are similar to the cells in the spinal fluid in herpes in man (Schottmüller).²⁴ The common occurrence in the spinal fluid of the streptococci in pure culture having affinity for the ganglia even when mixed cultures were injected is in accord with the finding of streptococci in the spinal fluid in one of our cases and in those of Achard and Loeper, Widal, and Brissaud-Siccard (cited by Oppenheim).¹⁰

The occurrence of relatively slight lesions in ganglia without peripheral herpes, adjoining those showing marked lesions accompanied by herpes; and the finding in the probable atrium of infection of bacteria having affinity for the posterior roots and ganglia in the patient who continued to have pain after the lesion of the skin had healed, and not

²⁴ Leitfaden zur Untersuchung der Zerebrospinalflüssigkeit, 1913.

in those patients who were free from pain, suggest strongly that the pain in post-herpetic neuralgia and allied conditions is due to active but slight infection of the ganglia or posterior roots. That these pains are not always due to scar tissue is certain, because Head and Campbell⁷ have found that ganglia corresponding to the area of herpes zoster may be largely replaced by connective tissue without the patient's suffering pain. The occurrence of herpes zoster in patients who have ulcer of the stomach (Case 281) or empyema is probably not a reflex arc effect or infection of the ganglia by way of the nerve lymphatics, as believed by Orr and Rowe,²⁵ but is due to a hematogenous infection from a focus harboring streptococci that have an elective affinity for the structures involved. The occurrence in 8% of the animals of ulcer of the stomach (proved to be due to local streptococcal infection in the mucous membrane following injection of these strains), is in line with this idea.

The fact that visceral herpes with accompanying lesions of the vagus and sympathetic ganglia has been produced experimentally, supports the view held by clinical observers that visceral herpes occurs in man, and since it occurred chiefly in animals with severe, usually fatal, bilateral herpes, it affords experimental evidence in favor of the general impression that bilateral herpes is apt to end fatally.

The absence of streptococci in the clear blister fluid both in man and in animals when the organisms are present in the ganglia, and the presence of pain before peripheral lesions can be made out, suggest that the lesions in the ganglia are primary, and that the peripheral manifestations—herpes of the skin, the tongue, the lip, and the viscera—are secondary trophic effects. The occurrence of herpes in cases of pressure-paralysis of the spinal cord would seem to be in accord with this idea. The finding of the streptococcus in the turbid bloody blister-fluid in one case of our series in man and in the severer peripheral lesions—skin, mucous membrane, tongue, and viscera—in experimental disease, the common occurrence of thrombosed blood vessels containing diplococci in both the peripheral and central lesions, and the absence of bacteria and demonstrable changes in the intervening nerve trunks, suggest strongly that while the primary milder lesions are trophic, making a "locus minoris resistentiae," the severer lesions, presenting as they do all the features of an infectious process, are the result of a superimposed hematogenous infection.

²⁵ Brain, 1914, 36, p. 271.

It is a noteworthy fact that of the large number of animals injected with cultures from a variety of diseases other than herpes,²¹ in which lesions resembling those in man have been produced, none has exhibited typical herpes.

Since the streptococci lose the characteristic affinity after cultivation on artificial media, after animal passage, and apparently in the focus of infection after recovery, the conclusion seems warranted that the atrium of infection is not only the place of entrance, but the place where the streptococci, by growth in symbiosis with other bacteria and under varying grades of oxygen-pressure, may acquire the peculiar properties necessary to infect in this particular manner.

It would appear, then, that herpes zoster is due to a streptococcus having elective affinity for the ganglia and the posterior roots. The possibility, however, that the disease in some instances may be due to other bacteria having a similar affinity must be admitted. (After this report was in proof, we found an abstract²⁶ of a paper by Raymond and Lot²⁷ which states that they cultivated a "cocco-bacillus" from the blood in 2 cases of herpes zoster, which when injected into rabbits and guinea-pigs, was followed by herpes and associated lesions of the corresponding ganglia. It is impossible to decide whether their organism is the same as ours, the original publication not being available.)

²⁶ Centralbl. f. Allgem. Path. u. Anat., 1915, 26, p. 501.

²⁷ Bull. et mem. d. soc. méd. d. Hôp. de Paris, 1913, 30.

EXPLANATION OF PLATES 8 TO 19

PLATE 8

FIG. 1. Herpes as seen on the under surface of the skin over the lower right thoracic region in a rabbit 24 hours after an intravenous injection of the streptococcus from herpes zoster (281). Note particularly the vesicular character of one of the lesions. Natural size.

FIG. 2. Herpes of the skin of the upper aspect of the right thigh of Rabbit 62, 48 hours after an intravenous injection of the streptococcus from the tonsil in Case 281. $\times 4$.

PLATE 9

FIG. 3. Thrombosis of the vein (a) and perivascular infiltration (b) of the posterior root adjacent to the ganglion corresponding to the area of herpes shown in Fig. 2. $\times 110$.

FIG. 4. Diplococci in a leukocyte within the thrombosed vein shown in Fig. 3. $\times 1200$.

FIG. 5. Diplococci in the hemorrhagic and infiltrated area surrounding the spinal nerve in the vertebral foramen corresponding to the area of herpes shown in Fig. 2. $\times 1200$.

PLATE 10

FIG. 6. Herpes of the skin over the left thorax of Dog 217, 48 hours after an intravenous injection of the streptococcus from the tonsil of Case 270. $\times 2\frac{1}{2}$.

FIG. 7. Leukocytic infiltration in and surrounding a ganglion (a) and thrombosis of the adjacent artery of the spinal ganglion (b) corresponding to the area of herpes shown in Fig. 6. $\times 65$.

PLATE 11

FIG. 8. Thrombosed blood vessel accompanying the posterior nerve root within the dura of the ganglion shown in Fig. 7. Note the large number of polymorphonuclear leukocytes. $\times 475$.

PLATE 12

FIG. 9.—Hemorrhage and leukocytic infiltration (a) of a spinal ganglion and of the associated nerve in Rabbit 47, 24 hours after an intravenous injection of the streptococcus from sputum in a case of severe thoracic herpes zoster (276). $\times 60$.

FIG. 10. Diplococci and streptococci in the infiltrated area shown in Fig. 9. $\times 1200$.

PLATE 13

FIG. 11. A number of the smaller areas of herpes of the skin over the thorax of Dog 225, 72 hours after an intravenous injection of the streptococcus from the tonsil in a case of severe thoracic herpes zoster (278). Natural size.

FIG. 12. Section of the skin through the area of herpes (Fig. 11) over the thorax in Dog 225, 72 hours after an intravenous injection of the streptococcus from the tonsil in Case 278. Note the desquamation of the epidermis (a) and the leukocytic infiltration (b). $\times 35$.

PLATE 14

FIG. 13. Marked herpes of the tongue in Rabbit 46, 24 hours after an intravenous injection of the streptococcus from a pyorrheal pocket in a case of severe thoracic herpes zoster (276). $\times 2\frac{3}{4}$.

FIG. 14. Section through a herpetic lesion at the tip of the tongue shown in Fig. 13. Note the hemorrhage and cellular infiltration (a), the ulceration (b), and the beginning thrombosis of an adjoining blood vessel (c). $\times 75$.

FIG. 15. Diplococci covering the base of herpetic ulcer of the tongue shown in Figs. 13 and 14. $\times 1200$.

PLATE 15

FIG. 16. Herpes of the tongue and of the mucous membrane about the teeth and lips in Rabbit 33, 24 hours after intravenous injection of the streptococcus from the tonsil in a case of recurring herpes (267). $\times 2\frac{1}{4}$.

FIG. 17. Section through a herpetic area of the lip of the rabbit shown in Fig. 16. Note the hemorrhage in the epidermis (a) and deeper layers of the skin (b), and the thrombosed blood vessel (c).

FIG. 18. Diplococci in the thrombosed blood vessel shown in Fig. 17 (c). $\times 1200$.

PLATE 16

FIG. 19. Hemorrhage (a) and round-cell infiltration (b) of the gasserian ganglion in Dog 299, 48 hours after an intravenous injection of the streptococcus from the tonsil in a case of lobar pneumonia with marked herpes of the lip and cheek (368). $\times 60$.

PLATE 17

FIG. 20. Herpes of the kidney of Rabbit 62, 48 hours after an intravenous injection of the streptococcus from the tonsil in Case 281. Note the numerous vesicles under the capsule. $\times 2\frac{1}{4}$.

FIG. 21. Section of the kidney shown in Fig. 19. Note the edematous areas (a), the compression of the glomeruli (b), and the swollen epithelium in the tubules with poorly staining nuclei (c).

FIG. 22. Diplococci in the hemorrhagic vagus ganglion of Rabbit 62, showing herpes of kidney shown in Fig. 20. $\times 1200$.

PLATE 18

FIG. 23. Herpes (a) of the lung in Dog 222, 48 hours after an intravenous injection of the streptococcus from the tonsil of Case 276. $\times 1\frac{1}{2}$.

FIG. 24. Section of the lung through the herpetic area shown in Fig. 23. Note the edematous fluid (a) and the hemorrhage (b) in the alveoli, and the absence of the pleura.

PLATE 19

FIG. 25. Hemorrhage (a) and leukocytic infiltration (b) in the sheath of the vagus just beyond the inferior vagus ganglion in Dog 225 showing visceral herpes 72 hours after an intravenous injection of the streptococcus from the tonsil in Case 278. $\times 110$.

FIG. 26. Photomicrograph of a 24-hour culture in ascites dextrose broth of a streptococcus isolated from the spinal fluid in a rabbit showing herpes after intravenous injection of a streptococcus culture from the tonsil in a case of herpes zoster in man (281). The morphology is characteristic of other strains as well. Gram stain. $\times 1200$.

PLATE 8

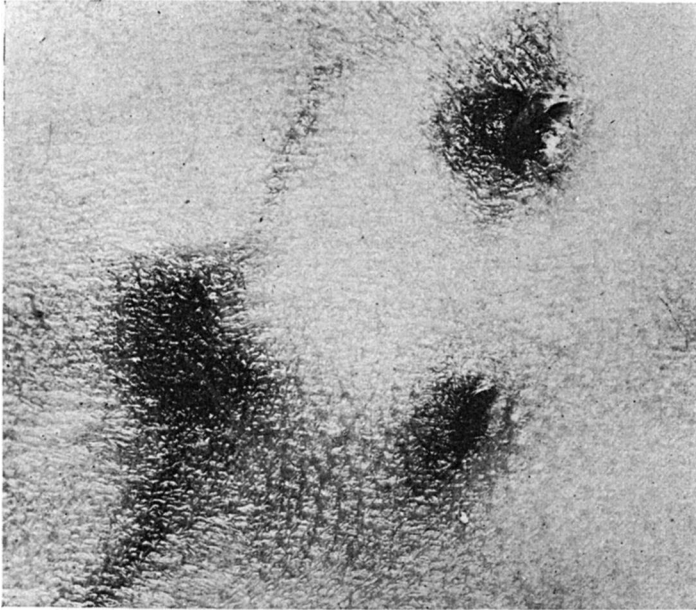


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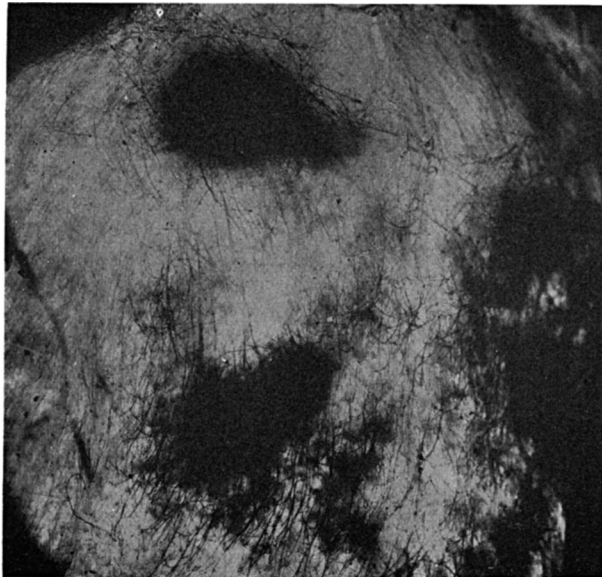


Fig. 2

PLATE 9

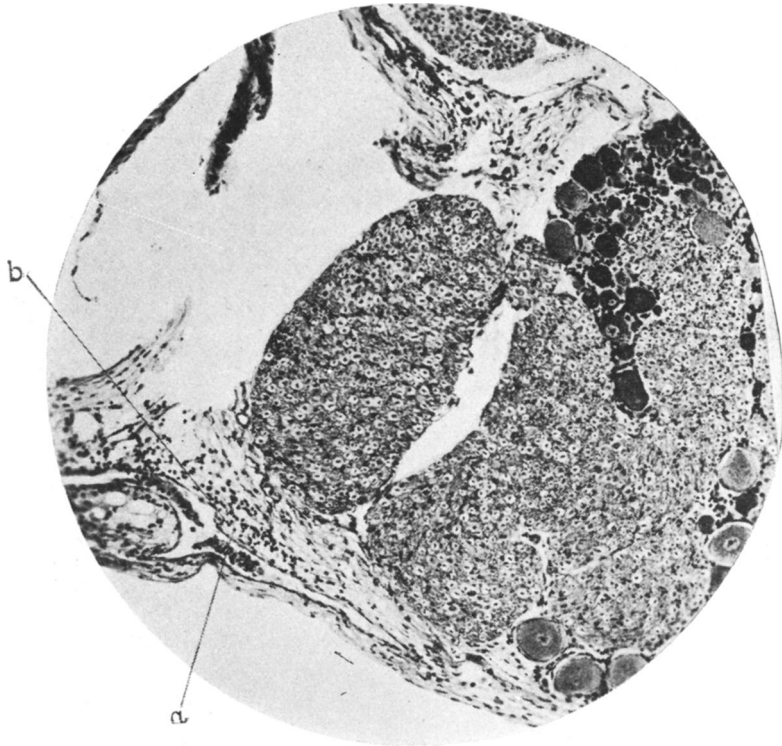


Fig. 3

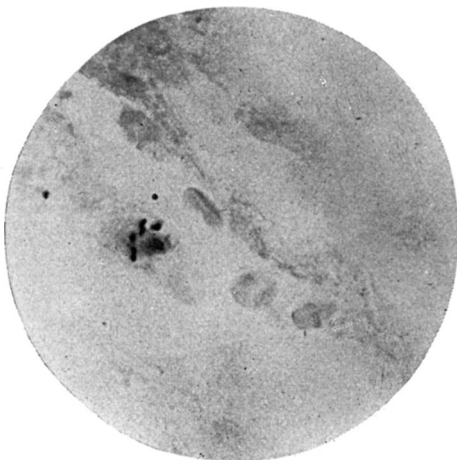


Fig. 4

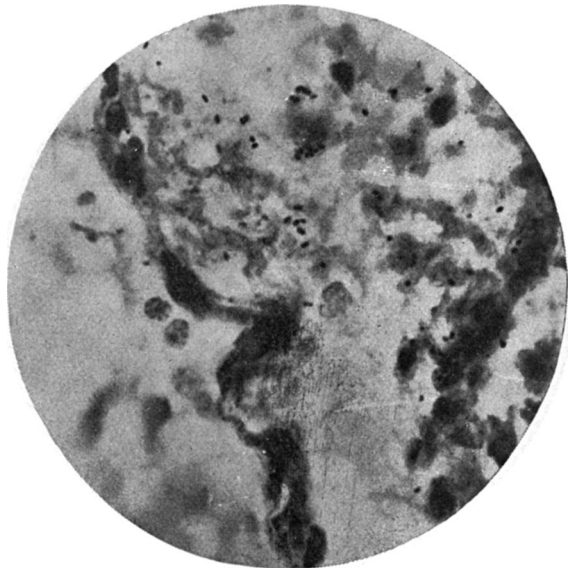


Fig. 5

PLATE 10

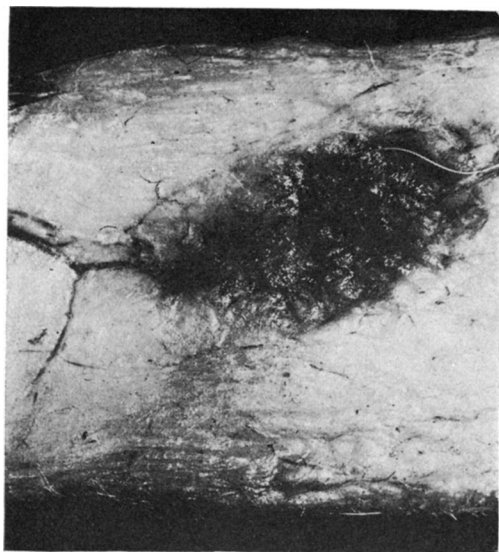


Fig. 6



Fig. 7

PLATE 11

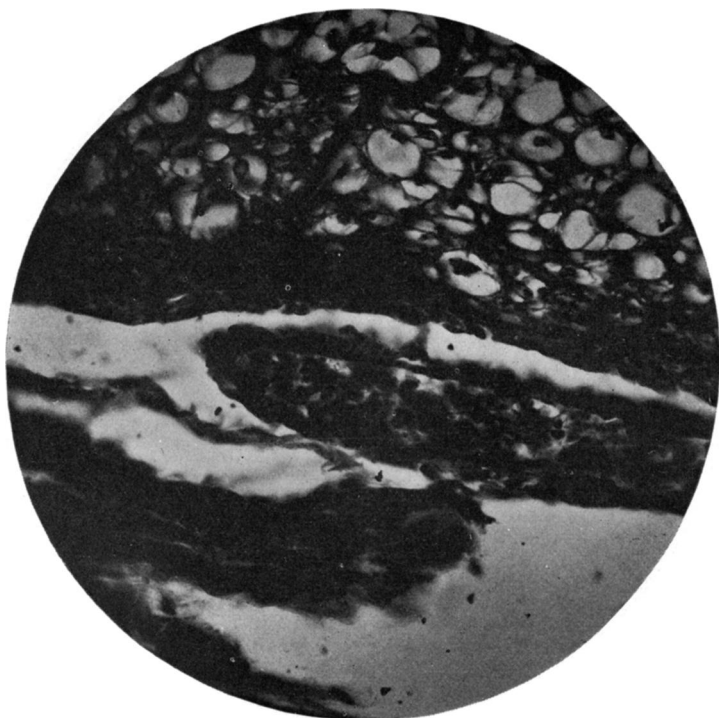


Fig. 8

PLATE 12

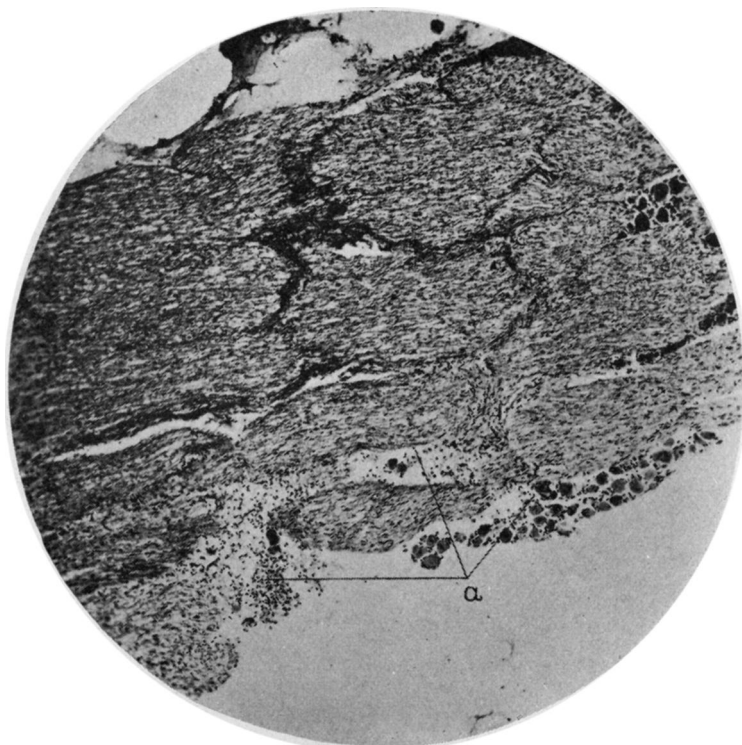


Fig. 9

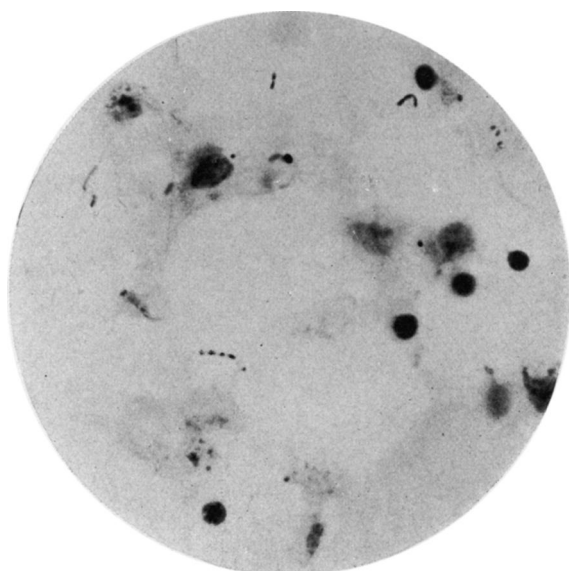


Fig. 10

PLATE 13

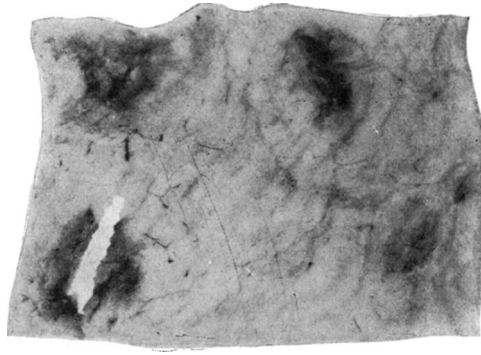


Fig. 11

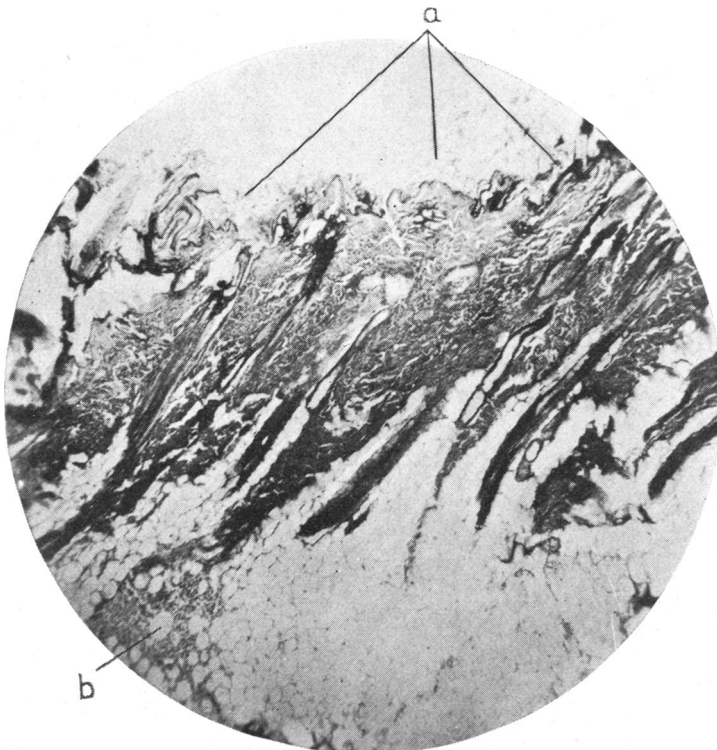


Fig. 12

PLATE 14

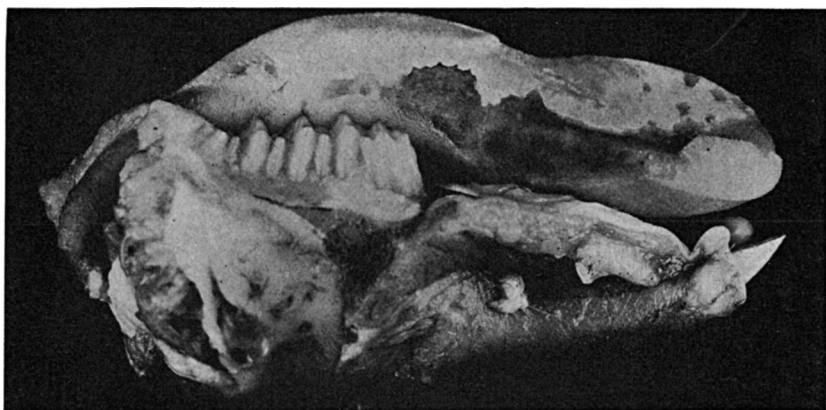


Fig. 13

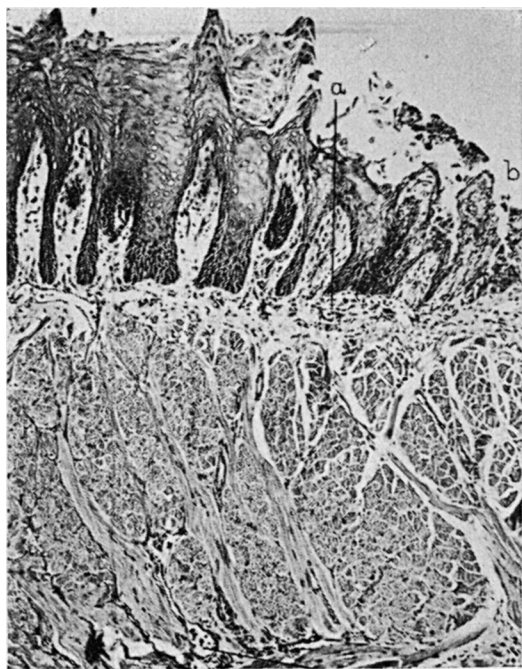


Fig. 14



Fig. 15

PLATE 15



Fig. 16

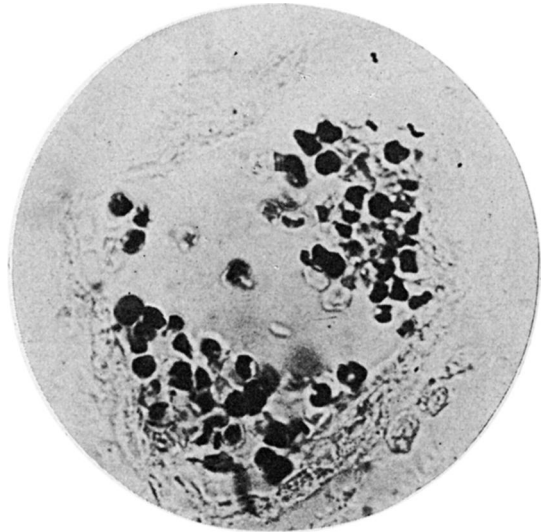


Fig. 18



Fig. 17

PLATE 16

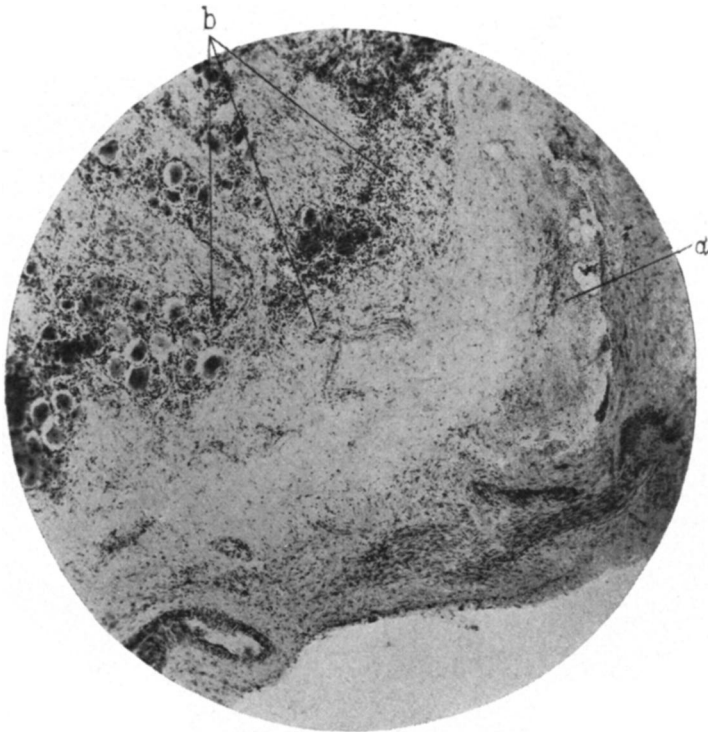


Fig. 19

PLATE 17



Fig. 20

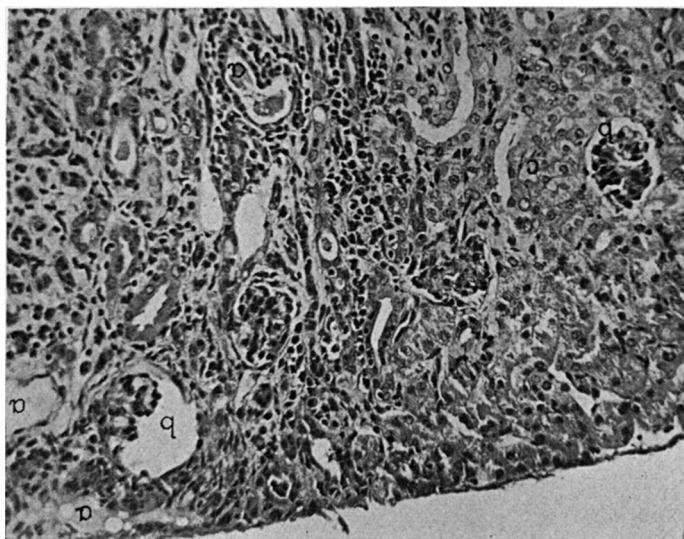


Fig. 21

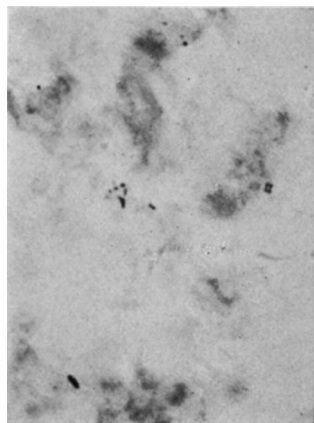


Fig. 22

PLATE 18

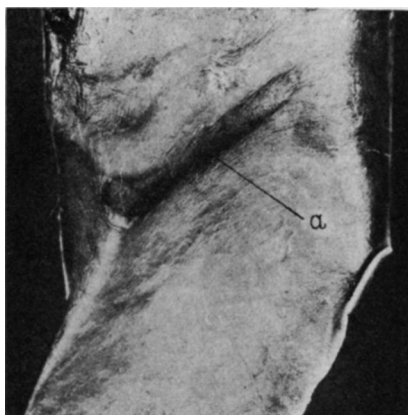
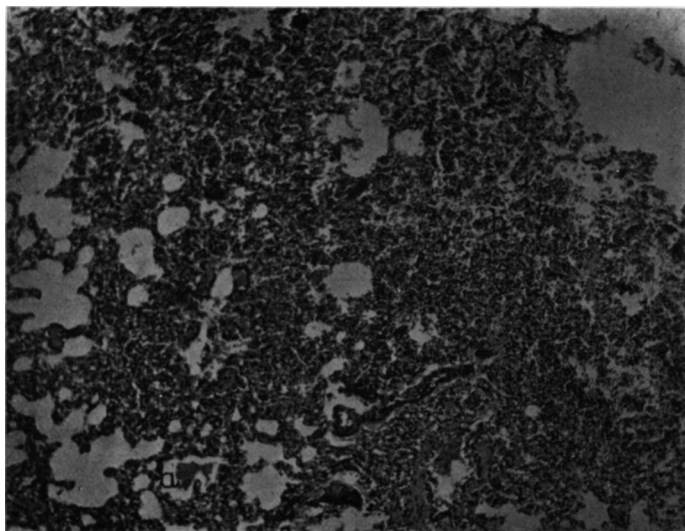


Fig. 23.



F.g 24.

PLATE 19

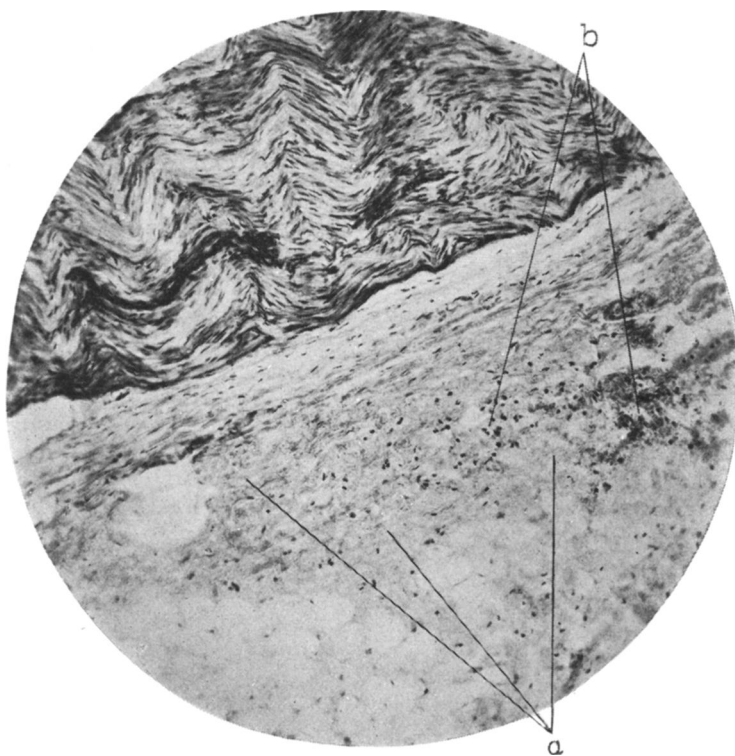


Fig. 25.

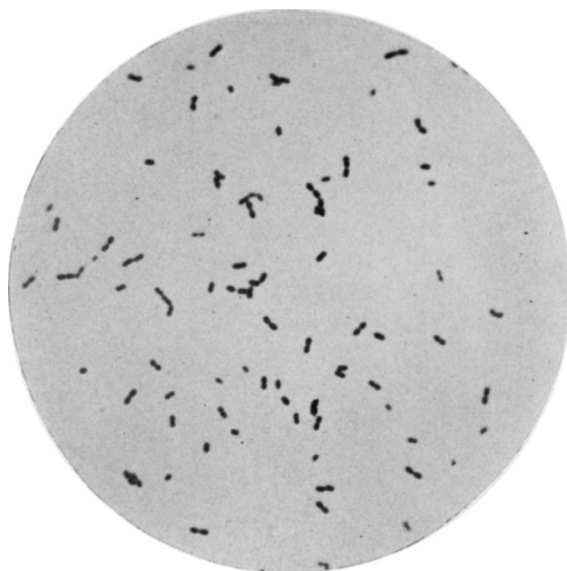


Fig. 26.